Amendments to the Claims:

Please cancel claims 35-43 and 48-52 without prejudice or disclaimer.

This listing of claims will replace all prior versions, and listings, of claims in the application:

Listing of Claims:

1-43. (canceled)

44. (currently amended) A transgenic mouse having a genome comprising ~~entirely~~ human heavy and light chain immunoglobulin variable region gene loci, wherein the human heavy and light chain variable region loci replace mouse endogenous heavy and light chain immunoglobulin variable region gene loci, and the human heavy and light chain variable region loci are ~~operably~~ linked to ~~entirely~~ endogenous mouse heavy and light chain immunoglobulin constant region gene loci to form hybrid loci, whereby the hybrid loci rearrange during B-cell development such that the mouse produces a serum containing an antibody comprising ~~a~~ human heavy and light chain immunoglobulin variable regions and ~~a~~ mouse heavy and light chain immunoglobulin constant regions in response to antigenic stimulation.

45. (currently amended) A transgenic mouse having a genome comprising a human heavy and/or light chain immunoglobulin variable region gene locus ~~loci operably linked to endogenous mouse immunoglobulin constant region gene loci such that~~, wherein the human variable region locus replaces an endogenous mouse variable region locus, and the human variable region locus is linked to an endogenous mouse immunoglobulin constant region to form a hybrid locus, whereby the hybrid locus rearranges during B cell development such that the mouse produces a serum containing an antibody comprising a human immunoglobulin variable region and a mouse immunoglobulin constant region in response to antigenic stimulation.

46. (currently amended) ~~A~~ The transgenic mouse of claim 44 or 45, ~~containing an~~ wherein the endogenous immunogobulin variable region gene locus ~~that~~ has been replaced with an homologous or orthologous human variable region gene locus~~, such mouse being produced by a method comprising:~~

~~a) obtaining a large cloned genomic fragment greater than 20 kb containing, in whole or in part, the homologous or orthologous human immunoglobulin variable region gene locus;~~

~~b) using bacterial homologous recombination to genetically modify the cloned genomic fragment of (a) to create a large targeting vector for use in the isolated mouse embryonic stem cells, the large targeting vector having homology arms totaling greater than 20 kb;~~

~~c) introducing the large targeting vector of (b) into the isolated mouse embryonic stem cells to replace by homologous recombination, in whole or in part, the endogenous immunoglobulin variable region gene locus; and~~

~~d) using a quantitative assay to detect modification of allele (MOA) in the mouse embryonic stem cells of (c) to identify those mouse embryonic stem cells in which the endogenous immunoglobulin variable region gene locus has been replaced, in whole or in part, with the homologous or orthologous human immunoglobulin variable region gene locus;~~

~~e) introducing the mouse embryonic stem cells of (d) into a blastocyst; and~~

~~f) introducing the blastocyst of (e) into a surrogate mother for gestation~~.

47. (currently amended) The transgenic mouse of claim 44 or 45 ~~or 46~~ wherein the endogenous light chain immunoglobulin constant region gene locus is a ~~the immunoglobulin variable region gene locus comprises one or more loci selected from the group consisting of:~~

~~a) a variable gene locus of the~~ kappa light chain locus~~;~~

~~b) a variable gene locus of the lambda light chain; and~~

~~c) a variable gene locus of the heavy chain~~.

48-52. (canceled)

53. (new) The transgenic mouse of claim 44 or 45, wherein the endogenous light chain immunoglobulin constant region gene locus is a lambda light chain locus.